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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,664	08/30/2001	David Botstein	P2548P1C8	2448

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BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, IL 60610

EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,664	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed December 21, 2004 has been entered.

Claims Status

2. Claims 25-34 are pending in the instant application. Claims 31 and 32 have been amended and claim 36 has been canceled as requested by Applicant in the Paper filed December 21, 2004.

Change of Inventorship

3. The request to correct inventorship filed December 21, 2004, has been entered.

Withdrawn Rejections

4.1 The rejections of claims under 35 USC § 102 as being anticipated by Holtzman et al., US Patent Application Publication US20020028508, is withdrawn, because the effective filing date of the reference is Feb. 21, 2001, because the disclosure is not enabling.

4.2 Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Claim Rejections - 35 USC § 101 and § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 25-34 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The basis for these rejections is set forth at pp. 3-7 of previous Office Action (Paper mailed March 24, 2003), at pp. 3-6 of Paper mailed March 17, 2004, and below.

Applicant's arguments (pp. 13-28, Paper filed 21 December 2004) have been fully considered but are not found to be persuasive for the following reasons.

To review prosecution briefly, the Examiner has made a prima *facie case* that the mild amount of gene amplification (approximately 2 fold to 4 fold) of nucleic acids encoding the claimed protein are not indicative of an increased amount of protein.

Applicants traverse the rejections and assert that as the polypeptides encoded by an amplified DNA sequence, the polypeptides have utility as diagnostic markers for determining the presence of tumor cells in lung and/or colon tissue samples. On page 14 of the response, Applicants submit that the Examiner sets the standard for satisfying the utility requirement too high, and that the references relied on by the Examiner, Pennica et al., Haynes et al. and Gygi et al., do not outweigh the evidence Applicants submit herein as support demonstrating that those

of skill in the art would reasonably expect the protein expression levels of the claimed polypeptides to correlate to the amplified levels of DNA. Applicants cite *In re Langer, In re Jolles, In re Irons and In re Sichert,* and submit that an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 USC § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." Applicants also assert that the credibility of the asserted utility is to be assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record. Applicants also cite *Raytheon v. Roper and In re Oetiker,* and submit that the evidentiary standard to be used throughout ex parte examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration, and thus to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Applicants cite *Nelson v. Bowler*, and submit that statistical certainty regarding Applicants' assertion of utility is not required to satisfy 35 USC § 101, and assert that a 35 USC § 101 rejection should only be sustained where the asserted utility violates a scientific principle or is *wholly* inconsistent with contemporary knowledge in the art (*In re Gazave*).

Applicants' arguments have been fully considered but are not deemed persuasive. While it is certainly credible that over-expression of mRNA could result in over-expression of the encoded protein, and statistical certainty is not required to satisfy 35 USC § 101, the Pennica et al., Haynes et al. and Gygi et al. references demonstrate that from the published literature in the field of mRNA expression and correlation with protein expression, there is not a strong

correlation between mRNA abundance and protein levels. *In re Gazave* differs considerably from the instant situation, because in that situation the Gazave application had a number of working examples that showed the effectiveness of an isoflavone compound having vitamin P activity in both animal and human studies. The examiner initially rejected the claims for "absence of clear, convincing, scientific evidence that the composition is safe and effective for all the purposes intended." He found "no showings in the case of statistically significant therapeutic treatments of vascular disorders, by the claimed methods, with lack of toxicity to the patient, when applied to humans and animals suffering from vascular disorders". An affidavit of Dr. Bernal conducting clinical trials with 44 humans was submitted, in which the patients treated with the compound in question, a lasting increase of capillary resistance was obtained in 91% of the cases with no side effects. After addressing other issues, the CCPA agreed with the Appellant that, "on the facts of this case, the Patent Office is in effect seeking to require too much proof of the asserted usefulness.", and "The additional affidavit evidence he has submitted is consistent with and convincingly corroborates those assertions." The instant application differs because there is not a single working example in the specification in which the polypeptide is demonstrated to be over-expressed in the tumor tissues, and there is no subsequent data supporting this assertion.

Applicants further submit that the totality of the evidence clearly demonstrates that the proposition that there will be correlation between protein and transcript level does not violate scientific principles nor it is wholly inconsistent with knowledge in the art. Applicants assert on page 16 of the response that according to Genes V, a central dogma of molecular biology is that genes are perpetuated as nucleic acid sequences, but function by being expressed in the form of

proteins, which are transcribed and then converted into protein (Lewin, Benjamin. Genes V. 1004). Applicants assert that those of skill in the art generally accept that gene expression levels correlate to protein expression levels absent specific events such as translation regulation, post-translation processing, protein degradation, protein isolating errors, etc, and refer to Ornтoft et al., and submit that Applicants' assertion that the claimed polypeptides are supported by a diagnostic utility because they are encoded by nucleic acids that are amplified in lung and colon tumors does not violate scientific principles.

Applicants' arguments have been fully considered but are not deemed persuasive. It is not disputed that genes are transcribed into RNA which is then translated into protein. However, specific events such as translation regulation, post-translation processing, protein degradation, protein isolating errors, ***are*** important in determining the final abundances of proteins. There is no evidence of record that that protein is present at elevated level, and the art would not lead to that expectation, as evidenced by Haynes and Gygi.

Applicant refers to six additional articles (Pollack, Ornтoft, Hyman, Bermont, Varis and Hu) as providing evidence that the utility of these claimed polypeptides is not wholly inconsistent with the knowledge in the art, and that one of ordinary skill in the art would reasonably conclude that the present invention is supported by a specific, substantial and credible utility.

Applicants on page 17 of the response discuss the Pollack et al. reference, which reports a parallel analysis of DNA copy number and mRNA levels, in which a significant fraction of highly amplified genes appear to be correspondingly highly expressed. Applicant characterizes Pollack et al. as teaching that 62% of highly amplified genes show moderately or highly elevated

expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels. However, Pollack et al. did not investigate polypeptide levels. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention.

Applicant characterizes Orntoft et al. as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts (CGH approach). Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. *could only compare the levels of about 40 well-resolved and focused abundant proteins* (see abstract), and do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40), whereas PRO347 in the instant specification was corrected for aneuploidy. Therefore, the relevance of Orntoft et al. is not clear. Additionally, in the abstract, Ornoft et al. states that "Because most proteins resolved by two-dimensional gels are unknown it was only possible to compare mRNA and protein alterations in relatively few cases of well focused abundant proteins." Haynes et al. and Gygi et al. also concluded that only the most abundant mRNAs correlated with a high level of protein, and from Table 10 in the specification it appears that PRO347 is not very amplified (ΔCt value of from 1.0 to 1.985) over normal tissue, so would appear not to fall into this category.

Hyman et al. used the same CGH approach in their research. Less than half (44%) of

highly amplified genes showed mRNA overexpression, and only 10.5% of *highly* overexpressed genes being amplified; thus even at the level of high amplification and high overexpression, the two do not correlate. Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support utility of the claimed polypeptides. Importantly, none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of **potential** cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965).

Applicant refers to Varis, Bermont and Hu as yet further examples that utility of the present invention based on a correlation between gene amplification and protein over-expression is not wholly inconsistent with knowledge in the art.

Varis studied copy number changes for 636 genes from chromosome 17q, which is amplified frequently in gastric cancer, and found increased copy numbers of 11 genes, 8 of which were found to be over-expressed in the expression analysis, demonstrating a 72% correlation between increased DNA copy number and gene expression level. However, protein expression was not investigated in this study, so that it cannot be determined from this if protein expression correlates with overexpression of the gene.

Bermont teaches that over-expression of p185 protein is usually associated with amplification of the encoding c-erbB-2 proto-oncogene. In breast cancer samples in which p185 is expressed at high levels, the oncogene was also amplified, whereas none of the p185 negative samples and 4% of p185 intermediate samples had an amplification of c-erbB-2. However, there

is no quantitative data presented, so it cannot be determined what degree of overexpression of the gene results in higher protein levels.

Hu et al. studied 588 well-characterized human genes involved in cancer and tumor biology using microarrays, and found that 18 of the 588 genes were identified to be differentially expressed (13 up-regulated and 5 down-regulated) in two newly established esophageal squamous cell carcinoma (ESCC) cell lines. The mRNA of oncogene MET was found to be overexpressed compared to a morphologically normal esophageal epithelium tissue from the patient which contributed one of the cell lines. This result prompted the authors to additionally examine MET protein expression in the two cell lines, the cell lines corresponding primary tissues and 61 primary ESCC tumors. The authors found that in 56 of 61 cases of ESCC (92%), MET protein was also overexpressed, and that MET overexpression had significant correlation with ESCC differentiation (Tables 3 and 4). In the discussion section (pages 3524-3525), Hu et al. discuss that the MET oncogene was originally identified as a tumor-transforming gene the encodes a tyrosine kinase receptor for hepatocyte growth factor, and that the vast body of clinical and experimental data has demonstrated that the MET oncogene plays a crucial role in tumorigenesis of many tumors, and has been found to be overexpressed in thyroid carcinomas, gastric carcinomas, colorectal carcinomas, ovarian carcinomas, endometrial carcinomas, pancreatic carcinomas, renal cell carcinomas, breast carcinomas and prostatic carcinomas. The authors also state in the paragraph bridging columns 1 and 2 or page 3524 that in this study the Cancer cDNA arrays hybridization revealed that oncogene MET mRNA was expressed at a much higher level in ESCC than in normal tissue (See Figure 1, panels A-C, spot 1). Therefore, authors found a correlation between mRNA levels of *one highly expressed mRNA* and increased

protein levels for an oncogene *known* to be involved in many different carcinomas. PRO347 is neither a known oncogene, nor overexpressed to the extent MET appears to be. It is known in the art that overexpression of growth factors or their receptors can result in uncontrolled cell growth, one of the trademarks of cancer. On the contrary, PRO347 is asserted in the specification to have (unspecified) homology to cysteine-rich secretory protein-3, which has no known activity. Applicants have provided no evidence of overexpression of the PRO347 protein in any of the tested cancer cells.

Applicants submit that although there may not always be a 100% correlation between gene amplification and protein over-expression, the above discussed references evidence that the utility of the present invention is not wholly inconsistent with the knowledge in the art, and therefore, also evidence that one of ordinary skill in the art would believe that the claimed invention is supported by a specific, substantial and credible utility. Applicants discuss the Pennica et al. reference, in which both WISP-1 and WISP-3 are amplified and which also had increased RNA expression, but WISP-2 was amplified but had significantly lower levels of RNA expression. Applicants point to page 1422 of Pennica et al., in which it is stated that because the center of the 20q13 amplicon has not yet been identified, it is possible that the apparent amplification observed for WISP-2 may be caused by another gene in this amplicon, and assert that because the RNA expression pattern of WISP-2 cannot be accurately attributed to gene amplification of WISP-2, this result should be disregarded.

Applicants' arguments have been fully considered but are not deemed persuasive. Even if it is established that genomic amplification results in over-expression of mRNA, such mRNA over-expression does not necessarily correlate with protein over-expression.

On pages 21-23, Applicants discuss the Haynes and Gygi references, and assert that they are not relevant here because they were not obtained in a human system, did not examine any particular human gene or protein expression, and most significantly, did not examine any genes that are amplified in a cancerous state. Applicants submit that Haynes and Gygi examine whether there is an overall system correlation between gene and protein expression levels, and in contrast, the present invention involves the correlation between expression levels of a single gene, the PRO347 nucleic acid and its encoded polypeptide, and that Gygi and Haynes report that for the entire group of genes, there was a general trend of increased protein levels resulting from increased mRNA levels. Applicants assert that the first set of genes, which are very low in abundance and which do not show a good correlation between mRNA levels and protein levels, should be disregarded, because the second group of genes, those of higher abundance and showing a good correlation between mRNA and protein levels, are more relevant to the present invention, which is directed to a polypeptide encoded by an amplified nucleic acid, and that Haynes and Gygi support the utility of the present invention.

Applicants' arguments have been fully considered but are not deemed persuasive. Analysis of the Haynes et al. and Gygi et al. papers shows that there is a positive correlation between only the most abundant mRNAs and protein expressed. However, the correlation coefficient for the whole data set of the Gygi paper, 0.935, was highly biased by a small number of genes with very large protein and message levels (page 1726). Genes for which the message level was below 10 copies per cell and included 69% (73 out of 106 genes) of the data used had a correlation coefficient of only 0.356. The Gygi paper also found that levels of protein expression coded for by mRNA with comparable abundance varied by as much as 30-fold and that the

mRNA levels coding for proteins with comparable expression levels varied by as much as 20-fold. As shown in Figure 6, the correlation value remained relatively stable in the range of 0.1 to 0.4 if the lowest expressed 40-95 proteins used in the study were included, but the correlation value steadily climbed by the inclusion of each of the 11 very highly expressed proteins. Therefore, the Gygi paper supports a positive correlation between mRNA expression and protein abundance only with **very highly** expressed mRNAs. The issue at hand in the instant application is whether protein is elevated and such elevation is detectable and correlative with a disease or disorder. Applicants have provided no data that would support their assertion that the amplified nucleic acid of SEQ ID NO: 49 would result in more protein. Therefore, one of ordinary skill in the art would not expect that protein from DNA amplified in a cancer would be expressed at a higher level. Absent any information about protein expression, it cannot be assumed that there is a difference in expression of the protein between normal tissue and tumors.

The results of Haynes and Gygi are further supported by Chen et al., Molecular and Cellular Proteomics, Vol. 1, pages 304-313, April 2002, who analyzed the abundance of 168 protein spots on two-dimensional gels corresponding to 98 individual genes in 76 lung adenocarcinomas and nine non-neoplastic lung tissues, and analyzed the abundance of the encoding mRNAs by microarrays and also measured protein abundance. They found that there was no significant correlation between mRNA and protein expression ($r = -0.025$, see abstract and page 311). Although 21/98 genes showed a statistically significant correlation between mRNA and protein, the majority of the proteins did not correlate with mRNA levels (page 311, first column). The authors suggest that in the first group, expression is likely to be regulated at the transcriptional level, while in the second group, expression is regulated by other mechanisms.

The authors also tested the global relationship between mRNA and the corresponding protein abundance using all 85 lung tissue samples, and observed a very wide range of normalized average protein and mRNA levels. The correlation coefficient generated was -0.025, and even for the 28 protein spots that showed a statistically significant correlation between individual mRNA and proteins, the correlation value was only –0.035. The authors suggest that it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples. Therefore, the art indicates that it is not the norm that increased transcription results in increased polypeptide levels.

Applicants on pages 23-25 define specific utility, substantial utility, credible utility and well-established utility and assert that as defined in the Revised Interim Utility Guidelines Training Materials, the claimed invention is supported by a utility that is specific, substantial, credible and well-established. First, while the asserted utility is credible, it is not specific, substantial or well-established, because significant further research would be required to determine if the protein was overexpressed in cancer tissue and could be used diagnostically. The Training Materials also state "Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities." The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides. For these reasons and those of record in the previous Office Actions, the rejection under 35 USC § 101 is maintained.

6.1 Claims 25-34 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants traverse the rejection and assert that as discussed in the response at pages 13-25, the claimed polypeptides are supported by the specific, substantial and credible utility of being therapeutic targets or diagnostic markers in lung or colon tumor tissues, which is supported by the Pollack, Ornoft, Hyman, Bermont, Varis and Hu references. However, as discussed above, the art as a whole does not support the assertion that gene amplification and overexpression of mRNA correlates with overexpression of protein. Therefore, the rejection under 35 USC § 112 is maintained.

Applicants further assert on pages 27-28 of the response that they have enabled the claimed invention commensurate with the scope of the present claims, and that one of ordinary skill in the art, reading the disclosure, would know to compare the claimed polypeptide with the sequence for the cysteine-rich secretory protein-3 and minimize amino acid changes in regions of high homology between the sequences, and additionally, the gene amplification assay that Applicants utilized for identifying and isolating the PRO347 nucleic acid and polypeptides can be used to test the ability of any variant sequence to encode a nucleic acid that is amplified in lung or colon tumors.

Applicants' arguments have been fully considered but are not deemed persuasive. The sequence alignment between the protein of SEQ ID NO: 50 of the instant invention and the human cysteine-rich secretory protein (attached) shows that there is very little homology

between the two proteins (9.9%), and one of ordinary skill in the art would not expect the proteins to have the same activity. Therefore, the sequence of the cysteine-rich secretory protein would not provide adequate guidance to introduce alterations.

6.2 Claims 25-26, 33 and 34 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants traverse the rejection at pages 32 of the response, and cite MPEP § 2163.02, and assert that they have satisfied the written description requirement because they have disclosed a combination of identifying characteristics sufficient to distinguish the claimed invention from other materials, and also maintain that the claimed invention satisfies the written description requirement under the analysis of Example 13 of the Training Materials which accompany the Written Description Guidelines.

Applicants' arguments have been fully considered but are not deemed persuasive. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factors present in the claim are functional, in that the the protein of SEQ ID NO: 50 is encoded by a nucleic acid that is amplified in lung or colon cancer. The specification discloses only a single sequence, SEQ ID NO: 50, that meets the limitations of the claims. It is clear that while there could be additional polypeptides that meet

the limitations of the claims, that conception of such polypeptides has not occurred, and cannot occur until their actual isolation, as it is not predictable what additional mutations in SEQ ID NO: 50 would occur in nature and further be associated with lung cancer. As previously stated, one cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQZII 1481 at 1483. In Fiddes, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. In this case, applicants have described a single sequence asserted to be associated with lung or colon cancer, and propose to obtain coverage for all related sequences that have a similar association. There is no description of that class of compounds. This case is also analogous to that in Amgen v. Chugai, 18 USPQ 2d 1017 (1991), in which it was found that conception may not be achieved until reduction to practice in cases involving cloning genes. In this case, applicants have no conception of which of the thousands of possible polypeptides and nucleic acids that could encode the protein of SEQ ID NO: 50 would meet the limitation of being amplified in lung or colon cancer.

Vas-cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method

of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. Chugai Pharmaceutical Co. L td.*, 18 USPQ2d 1016. Therefore, polypeptides comprising the sequence set forth in SEQ ID NO: 50, but not the full breadth of the claims meet the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 22-34 remain rejected under 35 U.S.C. 102(a) as being anticipated by Botstein et al., WO 99/35170, July 15, 1999, claims 22-27, 31, 33 and 34 remain rejected under 35 U.S.C. 102(a) as being anticipated by Holtzman, WO 99/54343, Oct. 28, 1999.

Applicants traverse the rejections and note that although the Holtzman et al. WO 99/54343 publication discloses an amino acid sequence that is 96.8% identical to SEQ ID NO: 50, it does not disclose any utility for that amino acid sequence, and submit that the declarations

of Botstein et al. overcome Holtzman et al. Applicants also submit that the declarations of Botstein et al. demonstrate that the nucleic acid and amino acid sequences of the present invention were completed prior to the effective date of the Botstein reference (filed 7/15/99), and that anticipation under 35 U.S.C. 102(a) requires that "the invention was ... patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent."

The declarations filed on December 21, 2004 under 37 CFR 1.131 have been considered but are ineffective to overcome the Botstein et al., WO 99/35170, and Holtzman, WO 99/54343 references. The rejections are maintained because Applicants have not signed the declarations. Upon submission of signed declarations, the rejections will be withdrawn.

It is believed that all pertinent arguments have been answered.

Conclusion

8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (571) 272-0829.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

Eileen B. O'Hara

EILEEN B. O'HARA
PATENT EXAMINER

1417	70.5	2.8	775	2	F98136 hypothetical prote
1418	70.5	2.8	788	1	I59282 diacylglycerol kin
1419	70.5	2.8	795	2	T20609 hypothetical prote
1420	70.5	2.8	800	2	AE3151 glucoamylase [impo
1421	70.5	2.8	837	1	A29512 LDL receptor precu
1422	70.5	2.8	865	2	B96558 probable protein k
1423	70.5	2.8	872	2	T30237 hypothetical prote
1424	70.5	2.8	873	1	QRRBVD VLDL receptor prec
1425	70.5	2.8	941	1	A55195 chordin precursor
1426	70.5	2.8	955	2	A45441 thrombospondin 4 -
1427	70.5	2.8	996	2	G87687 hypothetical prote
1428	70.5	2.8	1036	2	T17405 scavenger receptor
1429	70.5	2.8	1053	2	S46199 probable complemen
1430	70.5	2.8	1126	2	A96032 probable two-compo
1431	70.5	2.8	1209	2	A49440 chromosome disjunc
1432	70.5	2.8	1260	1	TVRTNU protein-tyrosine k
1433	70.5	2.8	1363	2	S44241 surface protein -
1434	70.5	2.8	1662	1	H71402 probable kinesin -
1435	70.5	2.8	2311	1	TVCHSR kinase-related pro
1436	70.5	2.8	2514	2	F81045 hemagglutinin/hemo
1437	70.5	2.8	2703	2	H81193 hemagglutinin/hemo
1438	70	2.8	94	2	C37057 fibronectin recept
1439	70	2.8	115	2	A96909 ferredoxin [import
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1444	70	2.8	258	2	A71282 conserved hypothet
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1449	70	2.8	335	2	T31560 hypothetical prote
1450	70	2.8	335	2	B82220 hypothetical prote
1451	70	2.8	340	2	S58770 cathepsin B (EC 3.
1452	70	2.8	372	2	H69426 probable transamin
1453	70	2.8	379	2	T40312 probable splicing
1454	70	2.8	391	2	AG3243 conjugal transfer
1455	70	2.8	405	1	JQ2386 3-oxoacyl-[acyl-ca
1456	70	2.8	405	2	T08521 tniQ protein homol
1457	70	2.8	414	1	S05441 cytochrome b5-rela
1458	70	2.8	419	2	T07817 S-locus-specific g
1459	70	2.8	421	2	T03421 traB protein - Agr
1460	70	2.8	425	2	T18592 hypothetical prote
1461	70	2.8	435	2	H72379 ammonium transport
1462	70	2.8	466	1	I46347 exo-alpha-sialidas
1463	70	2.8	474	2	A75276 sensor histidine k
1464	70	2.8	495	2	S32179 tniQ protein homol
1465	70	2.8	500	2	AE1963 hypothetical prote
1466	70	2.8	512	2	T37819 probable zinc meta
1467	70	2.8	525	1	S38794 cellulose 1,4-beta
1468	70	2.8	532	2	JC1392 monophenol monooxy
1469	70	2.8	532	2	JC5412 epidermal growth f
1470	70	2.8	540	2	B47417 insulin receptor-r
1471	70	2.8	588	2	T07085 probable lysine-tR
1472	70	2.8	600	2	T18593 hypothetical prote
1473	70	2.8	602	2	A96254 exsE protein (AJ22
1474	70	2.8	651	2	JC7705 death receptor-6 -
1475	70	2.8	686	2	AI0803 conserved hypothet
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1477	70	2.8	754	2	S47268 endothelin-convert
1478	70	2.8	758	2	A54667 endothelin convert
1479	70	2.8	777	2	I48100 ADAM 5 protein pre
1480	70	2.8	780	2	A48143 HF-1 regulatory el
1481	70	2.8	808	2	A41538 ATP-binding casset
1482	70	2.8	809	2	B83409 hypothetical prote
1483	70	2.8	847	2	D72860 viral capsid assoc
1484	70	2.8	859	2	S24571 env protein - huma
1485	70	2.8	942	2	S49109 spherulin - Melolo
1486	70	2.8	951	2	T45726 hypothetical prote
1487	70	2.8	961	2	E86245 hypothetical prote
1488	70	2.8	977	2	S49004 tyrosine kinase Mp
1489	70	2.8	1134	2	C88040 protein F47F6.5 [i
1490	70	2.8	1245	1	VHWVB2 structural polypro
1491	70	2.8	1252	2	S36016 oocyst wall protei
1492	70	2.8	1369	2	S70713 protein-tyrosine k
1493	70	2.8	1782	2	S45289 vitellogenin precu
1494	70	2.8	2470	2	I50726 cation-independent
1495	69.5	2.7	50	2	A48545 transforming growt
1496	69.5	2.7	147	2	A39091 phospholipase A2 i
1497	69.5	2.7	160	1	WFHU1 transforming growt
1498	69.5	2.7	165	2	E64758 membrane protein y
1499	69.5	2.7	172	2	E83264 hypothetical prote
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ALIGNMENTS

RESULT 1
S68691
neutrophil granules matrix glycoprotein SGP28 precursor - human
C;Species: Homo sapiens (man)
C;Date: 15-Feb-1997 #sequence_revision 13-Mar-1997 #text_change 09-Jul-2004
C;Accession: S68691; S74313; S68683
R;Kjeldsen, L.; Cowland, J.B.; Johnsen, A.H.; Borregaard, N.
FEBS Lett. 380, 246-250, 1996
A;Title: SGP28, a novel matrix glycoprotein in specific granules of human neutrophils w
A;Reference number: S68691; MUID:96186934; PMID:8601434
A;Accession: S68691
A;Molecule type: mRNA
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A;Molecule type: protein
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R;Kraetzschmar, J.; Haendler, B.; Eberspaecher, U.; Roosterman, D.; Donner, P.; Schleun
Eur. J. Biochem. 236, 827-836, 1996
A;Title: The human cysteine-rich secretory protein (CRISP) family. Primary structure an
A;Reference number: S68681; MUID:96270732; PMID:8665901
A;Accession: S68683
A;Status: preliminary
A;Molecule type: mRNA
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A;Cross-references: EMBL:X95240; NID:g1262818; PIDN:CAA64527.1; PID:g1262819
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C;Superfamily: cysteine-rich secretory protein 1
F;1-19/Domain: signal sequence #status predicted <SIG>
F;20-245/Product: neutrophil granules matrix glycoprotein SGP28 #status predicted <MAT>

Query Match 9.9%; Score 250; DB 2; Length 245;
Best Local Similarity 27.1%; Pred. No. 1.7e-11;
Matches 76; Conservative 44; Mismatches 108; Indels 52; Gaps 12;

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Qy         13 LLAVLLALLGTTWAEVWP--PQLQEQAPMAGALNRKESFL---LLSLHNRLRSWVQPPAA 67
Db          3 LFPVLLFLV----AGLLPSFPANEDKDPAFTALLTTQTQVQREIVNKHNELRRAVSPPAR 58

Qy         68 DMRRLDWSDSLAQLAQARAALCGI----PTPSLASGLWRTLQVGWNMQLLPAGLASFVEV 123
Db         59 NMLKMEWNKEAAANAQKWANQCNYRHSNPKDRMTS-----LKCGENLYMSSAP-SSWSQA 112

Qy        124 VSLWFAEGQRYSHAAGECARNATCTHYTQLVWATSSQLGCGRHLCSAGQTAIEAFVCAYS 183
Db        113 IQSWFDEYNDFDFGVGPKTPNAVVGHYTQVVWYSSYLVGCGNAYCPNQKVLKYYYVCQYC 172

Qy        184 PGGNWEVNGKTIIPYKKGAWCSLCTASVSGCFKAWDHAGGLCEVPRNPCRMSCQNHGRLN 243
Db        173 PAGNWA--NRLYVPYEQGAPCASCPDNCD---------DGLC---TNGCK---------- 208

Qy        244 ISTCHCHCPPGYTGRYCQVRCSLQCVHGRPREE-ECSCVC 282
Db        209 YEDLYSNCK--------SLKLTLTCKHQLVRDSCKASCNC 240
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